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Bisphenol A, Obesity, and Type 2 Diabetes Mellitus: Genuine Concern or Unnecessary Preoccupation?

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Abstract

Bisphenol A or BPA is a ubiquitous industrial chemical found in a variety of plastic containers intended for food storage and in the epoxy resin linings of metal food and beverage cans, where it is used to prevent corrosion, food contamination, and spoilage. BPA has been recently linked to a wide variety of medical disorders and is known to have estrogenic activity with genomic as well as non-genomic estrogen-receptor mediated effects. Given rapidly increasing prevalence rates of metabolic disorders like obesity and Type 2 diabetes, BPA has recently come under intense scrutiny in scientific and lay communities as a potential endocrine disrupting compound with diabetogenic effects. The purpose of this review is to critically examine available literature investigating the link between BPA and alterations in metabolic health. Here, we discuss typical levels of exposure to BPA in daily life and analyze both epidemiological human data and mechanistic preclinical studies that have tested associations between BPA and obesity and diabetes. Finally, we summarize the current policies and views of national and international regulatory agencies regarding the safety of BPA use.

Keywords

bisphenol A; diabetes mellitus; obesity

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Introduction

Diabetes mellitus is a disease of disordered glucose homeostasis that affects over 300 million individuals worldwide and roughly 26 million Americans. Type 2 diabetes (T2D) accounts for approximately 90 percent of all diabetes cases and is characterized by a combination of insulin resistance, impaired hepatic gluconeogenesis, and altered β cell function (1, 2). The prevalence of T2D in U.S. adults has nearly tripled since 1980 (3), and recent data suggest that T2D is increasingly prevalent among younger populations (4). These trends have largely been attributed to the growing and parallel epidemic of obesity. While overnutrition and lack of physical activity play a central role in the pathophysiology of obesity and diabetes, there is increasing attention in both scientific and lay communities regarding the effects of environmental toxins on overall metabolic health. Chemicals and pollutants such as lead, arsenic, polychlorinated biphenyls (PCBs), dioxins, dichlorodiphenyltrichloroethane (DDT), and phthalates have all been classified as potential endocrine disrupting chemicals (EDCs) (5, 6), which the World Health Organization (WHO) defines as any “exogenous substance or mixture that alters function of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations” (7, 8).

Bisphenol A or BPA is a ubiquitous chemical that is garnering focused scrutiny as a potentially diabetogenic EDC. BPA is an industrial chemical that has been widely used since the 1960s to produce plastics, where its primary purpose is to prevent damage to polycarbonate containers over multiple uses. BPA is also used in the epoxy resin linings of metal food and beverage cans to prevent corrosion, food contamination, and spoilage (9, 10). In 2012, the Food and Drug Administration (FDA) banned the use of BPA in products designed for infants and toddlers because of consumer concerns over its effects on neurological development in young children. However, the FDA presently maintains that small levels of BPA, such as those found in canned food, are safe for consumption (10). However, there is ongoing controversy regarding the background amount of BPA exposure in modern society as well as the establishment of safe levels of exposure. Despite the growing concerns surrounding BPA toxicity, a study by Transparency Market Research, suggests the demand for BPA in products has been increasing, and BPA sales are expected to grow to almost 19 billion dollars by the year 2019 (11). One of the reasons for this anticipated increase in BPA production is growing industrialization in many Asian countries, such as China (12). The goal of this review is to summarize human epidemiological and preclinical mechanistic studies that have investigated links between BPA and the development of glucose intolerance and obesity, suggest steps that can be taken to further research in this area, and provide ways in which consumers can minimize contact with BPA.

Human Exposure to BPA

Humans come in contact with BPA through residual industrial waste in air and water. However, the most common medium for BPA exposure is through consumption of food stored in BPA-containing containers. BPA found in the epoxy resin linings of metal cans

and in polycarbonate plastics can leach into the food or drink inside the container. The amount of BPA that migrates into food depends on the amount of BPA used to make the material, as well as the heating times and temperatures used to manufacture the container. Increased BPA has been shown to leach into food if the container is placed in a microwave for extended periods of time, or exposed to vegetable oil and/or sodium chloride solutions (13, 14).

Whether humans are exposed to enough BPA to cause ill effects is highly controversial, and there is disagreement surrounding how much BPA humans are exposed to on a daily basis. The FDA estimates that infants are exposed to 0.2–0.4 µg/kg of body weight of BPA per day, while children and adults are exposed to 0.1–0.2 µg/kg/day (10). On the other hand, the World Health Organization estimates that infants can be exposed to as much as 0.45–1.61 µg/kg/day and toddlers can be exposed to as much as 0.78 µg/kg/day (15). However, there is a general consensus that infants and toddlers are exposed to more BPA than adults on a regular basis. These differences may be secondary to increased levels of ingestion when normalized to body weight and an increased tendency for infants and toddlers to place objects in their mouths (16).

Data from the 2003–2004 US National Health and Nutrition Examination Survey (NHANES) demonstrated that approximately 90 percent of the U.S. population 6 years of age had detectable levels of BPA in their urine, with concentrations ranging from 0.4 µg/L to 149 µg/L. Children and adolescents had higher urinary BPA levels compared to adults, a finding consistent with increased levels of exposure (17). Important ethnic and socioeconomic differences have also been noted, and those in the lowest income categories had the highest levels of urinary BPA (18). BPA has also been detected in breast milk and fetal cord blood (19, 20).

Epidemiological data showing correlations between BPA, obesity, and diabetes

Over the past ten years, a number of studies have linked BPA to detrimental health effects that are broad in scope and include cancer, neurological disorders, and infertility (21–23). The correlation between urinary BPA concentrations from NHANES data and obesity and diabetes has been tested by a number of groups. Lang et al. analyzed the relationship between urinary BPA and diabetes using cross-sectional NHANES data from 2003–2004. They found higher levels of BPA were positively associated with a self-reported diagnosis of either diabetes or “borderline diabetes”. Citing some specificity to metabolic outcomes, the group did not find an association between urinary BPA and other chronic diseases such as asthma, cancer, or chronic bronchitis (24). Melzer and et al. subsequently analyzed data from the 2003–2004 and 2005–2006 NHANES datasets and found a significant association between urinary BPA levels and diabetes in pooled data. However, the association failed to maintain significance after analysis using fully adjusted models. Notably, the diagnosis of diabetes in this study was also by self-report and the presence of diabetes or “borderline” diabetes were combined into a single outcome (25).

Shankar and Teppala analyzed samples collected from adult NHANES participants between 2003–2008. In contrast to previous studies, the authors provided a more rigorous assessment of diabetes, which was diagnosed according to the American Diabetes Association standards of fasting blood glucose and hemoglobin A1c levels. This study also found a positive correlation between the diagnosis of diabetes and increased levels of urinary BPA in a pooled analysis (26). Similar findings were noted by Silver and colleagues, who also analyzed pooled data from the 2003–04, 2005–06, 2007–08 NHANES reporting periods. In this study, diabetes was defined as a hemoglobin A1c \geq 6.5% or through the use of anti-diabetic medications. Interestingly, when data from each of the three cycles was individually analyzed, the authors found the association was largely driven by the 2003–2004 data, where urinary BPA levels were noted to be the highest compared to the other time periods (27).

The same group of authors conducted another analysis of cross-sectional NHANES data (again 2003–2008) and interrogated correlations between BPA and metabolic syndrome (28). They found a positive association between higher urinary BPA levels and the prevalence of metabolic syndrome that was independent of other confounding factors such as age, diet, and race. In this analysis, the diagnosis of metabolic syndrome was based on revised Adult Treatment Panel III (ATP III) guidelines and included: increased waist circumference, elevated blood pressure, elevated serum triglycerides, glucose intolerance, and reduced HDL.

In contrast, LaKind et al. performed an updated analysis of all NHANES data collected between 2003–2010 and found no correlation between cross-sectional urinary BPA levels and a diagnosis of diabetes. Diabetes was diagnosed based on either a physician diagnosis of diabetes, fasting blood glucose $>$ 126 mg/dL, or a two hour blood glucose value $>$ 200 mg/dL following an oral glucose test (29).

The association between urinary BPA levels and obesity has been similarly tested using epidemiological data. Carwile and Michels analyzed cross-sectional pooled urinary BPA data from adult participants in the 2003–2004 and 2005–2006 NHANES cohorts. Compared to those with urinary BPA levels in the lowest quartiles, participants in the upper quartiles were significantly more likely to be obese and have abdominal obesity (30). Similar results were found in an analysis of 2003–2008 NHANES data, which tested the association between urinary BPA and obesity in children and adolescents. Children with the lowest quartile of urinary BPA levels were also noted to have the lowest rates of obesity (31). These findings were verified by a second group (32), and subsequent analysis of NHANES data from 2003–2010 has shown that higher levels of BPA are independently associated with obesity and abdominal obesity in children (33).

Epidemiological studies are increasingly being performed using datasets from other populations and ethnic groups. A recent study of over 1300 Chinese children in grades 4–12 investigated the relationship between urinary BPA and weight status. Overweight was defined as having a weight $>$ 90th percentile of the age and gender specific weight distribution. Results showed that higher urinary BPA was positively correlated with overweight status in peri-pubertal girls (aged 9–12 yrs). In this group, those with a urinary BPA level greater than or equal to 2 μ g/L had a two-fold increased risk of being overweight

compared to those with urinary BPA level <2 µg/L. Urinary BPA level was not associated with overweight status for older female students or male students (34)

Table 1 summarizes key epidemiological studies that have investigated associations between BPA, diabetes, obesity, and metabolic syndrome using NHANES data. The majority of these published studies have shown positive associations between diabetes, obesity, and the highest levels of urinary BPA. However, a number of caveats and controversies should be noted. While analysis of epidemiological data is hypothesis generating and may provide correlational links, these analyses have been unable to define causal relationships. Furthermore, most studies are performed using cross-sectional analysis of a single urine sample. To date, urinary BPA concentrations have not been followed longitudinally and linked prospectively to the development of either obesity and/or diabetes. Finally, there is tremendous controversy as to whether urinary BPA is able to even accurately assess level of exposure (35). A number of studies have shown that urinary BPA is reflective of recent dietary intake of BPA, but does not accurately reflect exposure at the tissue or serum level (36, 37). As such, a single cross-sectional urinary sample may not provide an integrated assessment of BPA exposure for any length of time.

Molecular and Mechanistic Links Between BPA, Obesity, and Type-2 Diabetes from Preclinical Studies

BPA action has been linked to a number of molecular targets with relevance to metabolic health and function. The chemical has been identified as a synthetic estrogen exerting estrogen receptor-mediated genomic and non-genomic effects, with activity at both estrogen receptor α and β (38). Studies generally indicate that BPA has generally weak estrogenic activity and binds receptors with 10,000–100,000-fold lower affinity compared to estradiol (39). BPA has also been demonstrated to have weak anti-androgen receptor activity (40). BPA stimulates glucocorticoid receptor (GR) activity in 3T3-L1 preadipocytes, suggesting another possible molecular link to obesity and adipogenesis. In the same study, however, BPA had no effect on PPAR- γ transcriptional activity (41). BPA has also been shown to act as a thyroid hormone receptor antagonist (39, 42). The variety of different molecular actions demonstrated by BPA strongly supports its classification as an endocrine disrupting chemical (EDC).

Preclinical studies as well as *in vitro* studies have been performed to provide additional mechanistic insight into the proposed relationship between BPA and obesity and glucose homeostasis. The majority of studies testing the effect of BPA on weight have employed perinatal treatment paradigms, where BPA has been administered to rodent dams during gestation and often lactation, and then sometimes followed by direct administration to offspring. These studies have yielded somewhat discrepant results, and BPA has been found to have obesogenic as well as weight-neutral effects. Results have varied based on a number of methodological considerations, which will be discussed in detail below.

An elegant study from Ryan et al. tested the effect of perinatal exposure of BPA in CD-1 mice. Dams were treated with 1 µg/kg/diet (1 parts per billion (ppb) or approximately 0.25 µg/kg of body weight/day from day e0 to p21 of gestation, which was felt to be an

“ecologically relevant dose”. Following delivery, one male and female pup from each litter were randomly selected for further study and then exposed to either low fat or high fat diet after 9 weeks of age. In pregnant dams, BPA increased food intake by 20% during days p14 to 21, and both male and female pups from BPA treated dams were heavier upon weaning. However, BPA had no effect on food intake or weight gain under high or low fat diet conditions in offspring followed out to 15 weeks of age. Furthermore, glucose tolerance was assessed by intraperitoneal administration of glucose and revealed no differences between groups (43).

Miyawaki et al. also conducted an *in vivo* study of perinatal and postnatal exposure of BPA in mice in order to test the effects of exposure on adiposity and obesity in offspring. In this study, pregnant ICR mice were exposed to BPA at a dose of either 1 µg/mL (low dose or LD) or 10 µg/mL (high dose or HD) in drinking water. After weaning, pups were then exposed to the same doses of BPA via drinking water. In female offspring, the mean bodyweight increase in the LD and HD groups were 13 percent and 11 percent respectively, with a mean increase in adiposity of 132 percent. In males, the mean body weight increase in HD group was 22% with a mean increase in adipose tissue weight of 59% (44). Rubin et al. and Somm et al. also conducted *in vivo* studies with similar results. In each case, increases in body weight and adiposity were observed. In these studies, the most prominent results observed in low-dose female groups (45, 46).

Alonso-Magdalena et al. tested the effect of 10 or 100 µg/kg/day from gestational day 9–15 in OF-1 mice. Glucose tolerance in pregnant dams was assessed during gestational day 16–18, and BPA-treated pregnant dams exhibited higher glucose excursions during an intraperitoneal glucose tolerance test. These findings were coupled with altered activation of insulin signaling pathways in liver and skeletal muscle in the low dose group. Mice treated with high dose BPA had an intermediate phenotype that was not statistically different from controls. Mice were then continued on BPA for 4 more months. Interestingly, mice treated with high dose BPA were heavier and demonstrated alterations in glucose tolerance. In contrast to results observed at the earlier time point, the low dose group was not different from untreated controls.

Male offspring were subsequently analyzed at 6 months of age. Interestingly, offspring from the low and high dose groups had equal degrees of glucose intolerance. The low dose group exhibited a decreased response to insulin during an intraperitoneal insulin tolerance test (ITT). Interestingly, the high dose group had a normal response during ITT, but exhibited an inadequate insulin secretory response both *in vivo* during the glucose tolerance test and *ex vivo* in isolated islets. These results suggest a component of pancreatic β cell dysfunction with high dose BPA exposure during gestation (47).

In another study, female offspring of CD-1 mouse dams exposed to 7.2 µg/kg/day of BPA, throughout gestation and lactation, were shown to consume excess kilocalories when exposed to high fat diet, leading to excess weight gain and adiposity compared to control mice. Male mice resisted weight gain but developed a greater degree of glucose intolerance. Interestingly, male and female mice also demonstrated distinct changes in gene expression in the arcuate nucleus of the hypothalamus. The authors reasoned that BPA may have direct

effects to alter hypothalamic energy balance (48). In contrast to the Miyawaki, Rubin, and Somm studies, effects were most prominent at higher doses with little effect noted at lower doses. In support of an obesogenic effect, BPA *in vitro* has been shown by several groups to directly promote adipocyte differentiation and stimulate 3T3-L1 cell differentiation into adipocytes (41, 49, 50).

In 2008, the National Toxicology Program and Center for the Evaluation of Risks to Human Subjects published a monograph that reviewed all available preclinical literature on BPA exposure. This document cited “insufficient evidence” to conclude that BPA exposure during development predisposed laboratory animals to obesity. This report also cited the lack of statistical or experimental control for litter effects as the single most common technical shortcoming in published studies. Because pups within the same litter may respond more similarly than pups from different litters, failure to adjust for litter effects may exaggerate differences between treatment groups (16). While a number of studies have positively linked BPA exposure to obesity, the vast majority of these studies have not controlled for litter effects (44–46). In contrast, the study by Ryan et al. found no association between perinatal BPA and metabolic outcomes including obesity or glucose intolerance. Notably, this study rigorously controlled for litter effects by only testing one male and one female pup from each litter and comparing multiple litters (43). However, it should be noted that the Ryan study did not test a wide range of BPA doses or level of exposure. An ideal experimental design might include a number of different doses and analysis of all offspring from a number of different litters.

BPA effects on insulin sensitivity and pancreatic β cell function

Notwithstanding controversies associated with the obesogenic effects of BPA in a developmental paradigm, the effects of BPA on insulin sensitivity and pancreatic β cell function have also been assessed in rodent models. BPA is thought to have genomic and non-genomic estrogen receptor-mediated effects, and estrogen is known to have important effects on both peripheral insulin signaling and β cell function (51). Mice were treated with 100 ug/kg/day of BPA for 8 consecutive days, which led to significantly increased levels of serum insulin and significantly decreased fed glucose levels compared to controls. Notably, glucose-stimulated insulin secretion in islets isolated from BPA-treated mice was also increased. Glucose tolerance was assessed by intraperitoneal glucose administration, and mice treated with BPA had similar levels of glucose tolerance compared to controls. However, BPA-treated mice had significantly worsened insulin tolerance as well as alterations in skeletal muscle insulin signaling, suggestive of impaired insulin sensitivity. While no change in body weight was noted over the eight-day study, BPA-treated mice also had decreased food intake and decreased activity levels (52).

Similar findings have also been noted in rats treated with BPA perinatally. Male offspring of Wistar rats treated with 50 ug/kg/day of BPA during pregnancy and lactation were hyperinsulinemic. The homeostatic model assessment (HOMA-IR) was used to assess levels of insulin resistance, and BPA-exposed rats were found to have significantly higher HOMA-IR values compared to controls, suggestive of worsened insulin sensitivity (53). Offspring of Wistar rats treated during gestation with 50 ug/kg/day of BPA were then fed normal or high-

fat diet after weaning. BPA and HFD-exposed male and female offspring had worsened glucose and insulin tolerance. While serum insulin levels were higher in BPA and HFD-exposed rats, their islets showed changes in mitochondria architecture, and ex vivo analysis of glucose-stimulated insulin secretion in isolated islets from male BPA and HFD-exposed offspring showed reduced insulin secretion at higher glucose levels. Notably, the authors of this study accounted for litter effects by analyzing multiple litters (54). Together, these studies indicate BPA may have effects to worsen insulin sensitivity. Interestingly, this is in contrast to estrogen, which is generally felt to improve insulin sensitivity (51).

To gain mechanistic insight into potential changes in molecular pathways that regulate insulin sensitivity, methylation status of the livers from BPA-treated mice were analyzed and found to have decreased global hepatic DNA methylation that occurred in parallel to changes in transcription of key metabolic genes like glucokinase (53). A transcriptomic analysis of BPA liver effects in CD1 mice and showed that BPA at a dose of 50 ug/kg/day increased liver fat and stimulated expression of a number of genes that increase hepatic lipogenesis (55). Furthermore, studies of cultured human adipocytes using BPA doses in the micromolar range demonstrate decreased release of adiponectin, a key insulin sensitizing adipokine, and increased release of pro-inflammatory cytokines that would be predicted to worsen insulin sensitivity (56). Similar findings have been noted in 3T3-L1 adipocytes where BPA at μM concentrations has also been shown to downregulate insulin signaling and AKT activation (50, 57). In contrast, 1 and 100 μM BPA increased insulin-stimulated glucose uptake in a different cell line, 3T3-F442A adipocytes, and this effect was independent of estrogen receptor activation. In aggregate, these data suggest that BPA effects might be difficult to model using transformed cell lines (58).

While changes in pancreatic β cell function have been noted in BPA-treated rodents, an important consideration is whether BPA has direct effects on the β cell or if observed changes in β cell function are secondary to alterations in insulin sensitivity. As described above, acute administration of BPA increased serum insulin levels in mice treated with 100 ug/kg/day. Similar findings were noted in by this group in earlier studies (47, 59, 60). To more directly address the effects of BPA, Soriano et al. treated mouse and human islets with 1 nM BPA and found the compound increased insulin release through a K_{ATP} -channel dependent mechanism. Intriguingly, effects were blunted in islets isolated from mice lacking estrogen receptor β , suggesting the effect of this compound may be through estrogen receptor signaling (60). Notably, estrogen is known to improve β cell function in diabetic models (61). Interestingly, higher doses of BPA have also been shown to increase human islet amyloid polypeptide toxicity in a rat insulinoma cell line (62), and in vivo studies continued for longer treatment periods have demonstrated some negative albeit subtle effects of BPA on β cell health (54).

Taken together, a number of rodent studies have demonstrated that BPA may negatively impact insulin sensitivity, though this has not been tested using rigorous methods like insulin clamps. These findings are somewhat in contrast to known effects of estrogen receptor activation on insulin sensitivity. While β cell secretory function and insulin release may be stimulated acutely by BPA, the long-term effects on β cell health with chronic treatment is unclear. Also, whether alterations in insulin sensitivity or β cell function occur

first is not certain, but should be tested in future studies using physiologically relevant treatment paradigms.

Potential Controversies Associated with Animal Studies

While pre-clinical *in vivo* studies are beginning to show positive links between BPA and effects on insulin sensitivity and β cell function, some caution should be taken when analyzing the literature and extrapolating findings to human populations. Firstly, humans are exposed to BPA through a variety of different ways (air, water, food, etc.). During *in vivo* testing, rodents are typically given controlled, oral doses of BPA at specific times each day; this model is highly unlikely when taking daily human life into consideration. Secondly, the design and study quality of published rodent studies varies widely with results varying based on a number of methodologic considerations including BPA dose and route of administration, duration or pattern of exposure, strain of rodent studied, route of administration, number of litters analyzed, inconsistent control for litter effects, the use of diets containing variable or unknown amounts of phytoestrogens, and the use of rodent cages that may contain variable amounts of BPA (8, 10). Some standardization of these variables should be attempted in future studies.

Response of Regulatory Agencies and the World Health Organization

The topic of BPA has been widely discussed in the lay press and BPA has been the subject of intense scrutiny by governmental regulatory agencies. The US FDA now requires products like baby bottles, which are intended for infant and toddler use to be BPA-free, and this decision was largely based over concerns about neurologic toxicity (10, 63). Aside from these specific products, the FDA and European Food Safety Agency (EFSA) have concluded that small amounts of BPA exposure for older populations that occurs through the use of plastic containers and food products is safe. The National Center for Toxicology Research likewise concluded that the transfer of BPA from mother to fetus from food products is so low that it cannot be reliably measured. The FDA does state on its web site that continued research and review of the literature will be performed and the agency will reconsider its stance as needed (10).

In our increasingly industrialized global society, BPA has also received attention from nongovernment organizations including the United Nations and the World Health Organization. In response to consumer concerns, the WHO and the United Nations Food and Agriculture Organization convened an expert panel to discuss BPA in 2010. After reviewing data from multiple different rodent and epidemiological studies, the panel concluded that BPA is a real concern for infants and toddlers with regard to neurological development, although only at high doses. However, the WHO similarly concluded there was no excess risk for other age groups exposed to very low doses of BPA on a regular basis. There was recognition of the potential for estrogenic effects. However, aside from encouraging continued research in this area, no further guidance was provided (8, 15).

Avoiding BPA in Daily Life

Notwithstanding current controversies from both clinical and preclinical studies, a prudent and practical approach to the uncertainty of BPA's global health effects may rationally involve the avoidance of unnecessary BPA exposure until more definitive conclusions can be made about the chemical's safety. Avoiding BPA in canned foods and plastics is a challenge because BPA is cheap and easy to produce and use. Companies such as Eden and Vital Choice have switched to BPA-free liners in canned foods. However, many companies do not label their canned products as "BPA-free," or "BPA-containing", which complicates this challenge for many consumers (64). The best way to avoid BPA is to minimize plastic use. Using glass or stainless steel cooking ware are convenient and safe alternatives (65). Avoiding plastic completely is a lofty task, and plastic containers are often the most convenient and cheapest choice for food storage. In general, plastics marked with recycle codes 3 or 7 are more likely to contain BPA than plastics marked with other codes. Also, avoid placing plastic containers into a microwave or storing in areas of extreme heat (e.g. inside a car), as this can increase the amount of BPA that leaches into food stored in the container (65). The FDA also recommends that all bottles with scratches be discarded, as they may harbor bacteria and lead to greater release of BPA.

Conclusions

BPA is a ubiquitous, industrial chemical that can be found in a wide variety of plastic food containers and metal cans. For over fifty years, the plastic industry has relied on this compound to enhance the durability and longevity of plastic containers. Exposure to BPA has been shown to hinder the neurological development of small children and infants, and led to recent FDA regulations mandating its removal from baby products. However, the question of whether small doses of BPA impact the development of obesity and diabetes in children and adults is the subject of active research, intense scrutiny, and a large amount of controversy and uncertainty. Analyses of cross-sectional data from epidemiological studies testing have largely shown positive associations between urinary BPA levels and metabolic diseases such as obesity and diabetes. However, there are a number of caveats that exist with extrapolating integrated levels of exposure to a single cross-sectional urinary sample. Preclinical studies have yielded conflicting results, but there is some recent indication that BPA may impact insulin sensitivity and β cell function in rodents. The applicability of these models to human health is not clear. BPA's contribution to the development of obesity in rodent models is also unclear. The most rigorously performed studies do not indicate an effect BPA on the development of obesity in offspring exposed to BPA perinatally. The only consensus that currently exists among the lay, scientific, and regulatory communities is that further study is needed determine the full extent of BPA's impact on human health and metabolic outcomes. The necessity to perform this research in a rigorous and standardized fashion is paramount, and there is a need for leaders in the field to participate in the establishments of guidelines for BPA testing in laboratory models. In human populations, longitudinal data that accurately defines levels of tissue BPA exposure coupled with prospective measures of disease development is urgently needed.

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Abbreviations

BPA	bisphenol A
FDA	Food and Drug Administration
EPA	Environmental Protection Agency
WHO	World Health Organization
EFSA	European Food Safety Agency
NHANES	National Health and Nutrition Examination Survey
HFD	High-Fat Diet
EDC	Endocrine-Disrupting Chemical
DDT	Dichlorodiphenyltrichloroethane
PCB	Polychlorinated Biphenyls
T2D	Type-2 Diabetes
LD	Low Dose
HD	High Dose
ICR	Imprinting Control Region
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
DNA	Deoxyribonucleic Acid

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Table 1

Urinary BPA and metabolic correlations from NHANES data

Author and Year	NHANES Cohorts Studied	Results
Lang et al., 2008 (24)	NHANES data from 2003–2004	<ul style="list-style-type: none"> • Positive correlation between urinary BPA levels and prevalence of diabetes and prediabetes by self-report.
Melzer et al., 2010 (25)	NHANES data from 2003–2004; 2005–2006	<ul style="list-style-type: none"> • Positive correlation found between urinary BPA and diabetes and pre-diabetes diagnoses by self-report in pooled data. • The association failed to reach significance after analysis using the fully adjusted model.
Shankar & Teppala, 2011 (26)	NHANES data from 2003–2004; 2005–2006; 2007–2008	<ul style="list-style-type: none"> • Diabetes was diagnosed based on fasting blood glucose and HbA1c; urinary BPA levels were positively correlated with a diagnosis of diabetes.
Silver et al., 2011 (27)	NHANES from 2003–2004; 2005–2006; 2007–2008	<ul style="list-style-type: none"> • Higher urinary BPA concentrations were positively associated with the prevalence of diabetes
LaKind et al., 2012 (29)	NHANES from 2003–2004; 2005–2006; 2007–2008; 2009–2010	<ul style="list-style-type: none"> • Urinary BPA content was not significantly associated with diabetes.
Carwile & Michels, 2011 (30)	NHANES data from 2003–2004; 2005–2006	<ul style="list-style-type: none"> • A positive correlation between urinary BPA and prevalence of obesity and abdominal obesity in adults was noted.
Trasande et al., 2012 (31)	NHANES 2003–2004; 2005–2006; 2007–2008	<ul style="list-style-type: none"> • Urinary BPA concentration in children and adolescents was significantly associated with obesity.
Bhandari et al., 2013 (32)	NHANES 2003–2004; 2005–2006; 2007–2008	<ul style="list-style-type: none"> • Urinary BPA concentration in children and adolescents was significantly associated with obesity.
Eng et al. 2013 (33)	NHANES 2003–2004; 2005–2006; 2007–2008, 2009–2010	<ul style="list-style-type: none"> • Urinary BPA concentration in children and adolescents was significantly associated with obesity and waist circumference.
Shankar, Madhavan, Teppala (2012) (28)	NHANES 2003–2004; 2005–2006; 2007–2008	<ul style="list-style-type: none"> • Urinary BPA concentration in adults was significantly associated with metabolic syndrome.